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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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VARNDELL & VARNDELL, PLLC
106-A S. COLUMBUS ST.
ALEXANDRIA, VA 22314

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,933	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56 and 58-86* is/are pending in the application.

4a) Of the above claim(s) *1-36,41-56,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-40 and 60-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-1-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-56, 58-86 are currently pending in this application. Claims 37-40 and 60-86 are now under consideration. Claims 1-36, 41-56, 58-59 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 7-22-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn the previous rejections under 35 U.S.C. 101 and 35 U.S.C. 112, 2nd paragraph in view of claim amendments. Examiner has also withdrawn the rejection of claims under 35 U.S.C. 102(b) as being anticipated by Schulein et al. (WO94/07998, April, 1994) or rejected under 35 U.S.C. 102(e) as being anticipated by Schulein et al. (US 6,387,690 5-14-2002) in view of claim amendments. The rejections of claims 37-40, 72-73, 86 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Somkuti (J. Gen. Microbiol., 1974, Vol. 81, pages 1-6) has also been withdrawn in view of the claim amendments and applicant's showing that the enzymes disclosed by Somkuti were not active in alkaline pH range. However, new rejections are in place.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claim 37 recites the phrase "alkaline conditions". While the meaning of the phrase as such is clear to the Examiner, (i.e., alkaline conditions are conditions wherein the pH of the composition can be above pH 7.0 and below pH 14), the metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. What specific pH values are encompassed in the above phrase is not clear to the Examiner.

Claim 60 and claims 61-85 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 60 continues to recite the limitation "protein, modified protein or homologue according to claim 40" in line 3 while such phrase has been deleted in claim 40. There is insufficient antecedent basis for this limitation in the claim. Furthermore, separately, claims 61, 71-79, 81—85 also independently recite the above phrase which lacks antecedence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-39, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an endoglucanase enzyme with SEQ ID NO:1, 3, 5, 7, 9 or 11, encoded by polynucleotides with SEQ ID NO:2, 4, 6, 8, 10 or 12 or 13 retaining endoglucanase activity under alkaline conditions, does not reasonably provide enablement for any or all endoglucanases produced by either *Rhizopus*, *Mucor* or *Phycomyces*, having a CBD

in the N-terminal region and being active in alkaline conditions, including mutants, variants and recombinants, and polynucleotides encoding such endoglucanases (including polynucleotides which comprise a sequence in which codons have been optimized for a host by selecting frequently used codons of that host), methods of using such enzymes and compositions comprising such enzymes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 37-39 are so broad as to encompass any endoglucanase from any member of the extremely large group of fungi classified as *Rhizopus*, *Mucor* or *Phycomyces*, including modified endoglucanases such variants, mutants or recombinants or homologues, wherein said enzymes are active in the broad range of pH 7.0 to pH 14.0 (alkaline conditions). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of endoglucanases active in alkaline conditions broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard

to which amino acid/s in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the endoglucanases with amino acid sequence SEQ ID NO:1, 3, 5, 9, or 11. Furthermore, while applicants have taught the polynucleotides with SEQ ID NO:2, 4, 6, 8, 10, 12, or 13, they have not taught polynucleotides encoding endoglucanases in which codons are optimized for any or all the host cells one of skilled in the art can use or to modify endoglucanase isolated from any one of the above species active in certain pH range (say for example pH 7.5-8.5) to be active in the whole alkaline range of pH (pH 7.0 to pH 14). It would require undue experimentation of the skilled artisan to make said endoglucanases and use the claimed polypeptides and polynucleotides. The specification is limited to teaching use of SEQ ID NO: 1, 3, 5, 9, or 11 encoded by SEQ ID NO:2, 4, 6, 8, 10 12, or 13 as a endoglucanase but provides no guidance with regard to the making of variants and mutants and homologues or with regard to the proteins comprising above sequences (with no specified activity) or other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any endoglucanase active in the alkaline pH range, obtained from *Rhizopus*, *Mucor* or *Phycomyces*, or endoglucanase with SEQ ID NO: 1, 3, 5, 9, or 11 and their respective polynucleotides encoding the same because the specification does not establish: (A) regions of the protein structure which may be modified without effecting endoglucanase activity such that said activity is exhibited at any alkaline pH value; (B) the general tolerance of endoglucanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any endoglucanase amino acid residue with an expectation of obtaining the desired biological function; (D) methods to optimize codons for use in any or all types of host cells; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including endoglucanases with an enormous number of amino acid modifications of the endoglucanase of SEQ ID NOS:1, 3, 5, 9 or 11 and the polynucleotides

encoding such enzymes. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of endoglucanases and their respective polynucleotides encoding the same having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant submits that claim 40 has been amended by deleting the expression "or a modified protein exhibiting endoglucanase activity and having a modification such as an addition, insertion, deletion or substitution of one or several amino acids" and therefore the rejection is moot as far as claims 40, 60-85 are concerned. Examiner agrees with such an argument and has removed claims 40 and 60-85 from the rejection.

With regard to claims 37-39 applicant has traversed the above rejection arguing that claim 37 recites specific criteria for the claimed endoglucanases regarding the CBD location and the retaining of the activity under alkaline conditions and that unlike what is argued n the previous Office action, any enzyme that does not meet the above limitation falls outs side the scope of claims 37-39. Examiner respectfully disagrees with such an argument as being persuasive to overcome the above rejection. This is because, irrespective of the limitations such belonging to family 45 and being isolated from *Rhizopus*, *Mucor* or *Phycomyces* and position of CBD, claims are still drawn to all enzymes including variants, mutants and recombinants that exhibit the activity under alkaline conditions (i.e., activity in a very broad pH range of anywhere

from pH7.0 to pH 14). Unless applicant specifies a specific and practical alkaline pH range, said claims are broadly interpreted as comprising all variants and mutants.

Next, applicant also argues that the specification provides numerous instances of amino acid modifications as well as reasoning for modifying the enzyme to guide the ordinary artisan. Examiner respectfully disagrees that such an argument would be persuasive to overcome the rejection. This is because, while the specification may provide a general example of modifying asparagines for linking oligosaccharide chains, it still does not provide guidance as to which specific asparagine it is (residue number). Furthermore, for the sake of argument even if applicant has provided any specific example for modifying any such single amino acid, then Examiner would be willing to consider that specific modified enzyme as being enabled. However, no such specific guidance or a specific modified amino acid sequence has been provided. Therefore, contrary to applicant's argument, the specification lacks guidance to make all the endoglucanase sequences as encompassed by the claims. Hence the above rejection is maintained. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. Therefore the above rejection is maintained.

Claims 37-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 37-39, are directed to endoglucanases from *Rhizopus*, *Mucor* or *Phycomyces* active in alkaline conditions and the respective polynucleotides encoding the same. Claims 37-39, are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides and polynucleotides derived from fungi or derived from SEQ ID NO:1, 3, 5, 7, 9, or 11 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue such that they are active in alkaline range of pH and that have not been disclosed in the specification. No description has been provided of the modified/homologue polypeptide and polynucleotide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:1-12 and 13 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides and polynucleotides encoding the same. The specification does not contain any disclosure of the structure of all the polypeptide sequences isolated from *Rhizopus*, *Mucor* or *Phycomyces* and having endoglucanase activity in the alkaline range and polynucleotides encoding the same within the scope of the claimed genus. The genus of polypeptides claimed and their respective polynucleotides encoding the same is a large variable genus including peptides/polynucleotides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides and polynucleotides are encompassed within the scope of these claims. The specification discloses only few species of the claimed genus which is

insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traversed the above rejection arguing that the amendment of claim 40 renders the rejection moot as applied to claims 40, 60-85 and provides ample description for the endoglucanases claimed in claims 37-39. Applicant also argues that given the methods outlined in the specification for enzyme activity measurement, partial amino acid sequencing, isolation of a coding sequence including primer selection, library screening, means for identifying enzyme activity and consensus sequences, the ordinary artisan would have a reasonable expectation of success and given the descriptions in applicant's specification disclosure, even if it was necessary for one of ordinary skill in the art to perform a substantial amount of experimentation that would require a fair amount of time; such experimentation would not amount to undue experimentation, because the person of ordinary skill in the art following the present specification disclosure has a reasonable expectation of success of identification of additional CBD containing sequences using these disclosed methods. Examiner respectfully disagrees with such arguments as being persuasive to overcome the written description requirement rejection. This is because applicant appears to argue the rejection as if it was directed to enablement. However, it is pointed out that the rejection is directed to written description requirement and applicant's claims are directed to a genus of

endoglucanases that are active in the full range of alkaline pH and whose structure has not been described. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one, two or three species within the genus. In the instant case the claimed genera of claims 37-39, includes species which are widely variant in structure. The genus of Claims 37-39, are structurally diverse as it encompasses polypeptides with endoglucanase activity in the broad alkaline range of pH. As such, the description of solely functional features present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37-39, are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al. (US 4,966,850, Oct 30, 1990). This rejection is based upon the public availability of a patent. Claims 37-39, of the instant application drawn to endoglucanases active in the alkaline range of pH, obtained from filamentous fungi and belonging to family 45, having a CBD in its N-terminal region, wherein the filamentous fungi belong to genus *Rhizopus*, *Mucor* or *Phycomyces* and a composition comprising said enzyme. Yu et al. disclose an endoglucanase composition isolated from *Mucor sp.* (see column 14, and Tables 9 through 11). While the reference does not explicitly disclose that the endoglucanase belongs to family 45 or that it has an N-terminal CBD, Examiner takes the position that the enzyme disclosed in the reference and that claimed are inherently one and the same as the reference enzyme is isolated from *Mucor sp.* Therefore, Yu et al. anticipate claims 37-39 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

In response to the previous Office action, applicant has traversed the above rejection arguing that Yu et al. discloses enzymes which exhibit low levels of activity at alkaline pH and therefore the enzymes of Yu et al. are patently distinct from that of the present invention. Examiner respectfully disagrees with such an argument as being persuasive to overcome the above rejection. This is because, contrary to applicant's argument, the enzyme of Yu et al. "retains 20% activity under alkaline pH conditions (see figure 3)" and instant claims are simply directed to endoglucanases "retaining endoglucanase activity under alkaline conditions". As there is no limitation in the claims regarding % activity retained under alkaline conditions, the reference meets said limitations of the claim and therefore anticipates claims 37-39.

Therefore, Examiner maintains that irrespective of the differences pointed out by the applicants, Yu et al. continue to anticipate instant claims as written.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 6.30 a.m. to 3.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao
September 27, 2004